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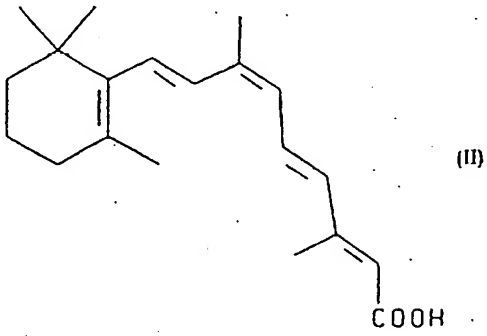
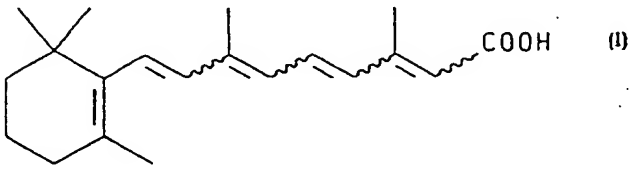
(54) Title: METHOD FOR THE PREPARATION OF 9-CIS RETINOIC ACID



(II)



(I)

(57) Abstract

A method for preparing a compound of formula (II) comprising photolyzing a compound of formula (I).

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METHOD FOR THE PREPARATION OF 9-CIS RETINOIC ACID

Background of the Invention

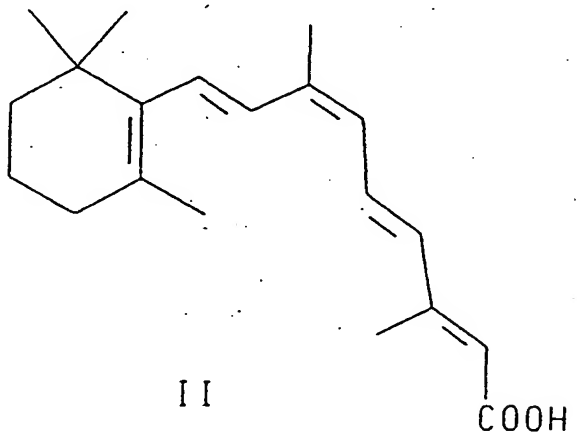
The present invention relates to a process for the preparation of 9-cis retinoic acid. That compound is useful in the treatment of dermal, neoplastic and immunological disorders.

Traditionally, 9-cis retinoic acids have been obtained as a result of non-selective olefination reactions in retinoic acid syntheses. J. Am. Chem. Soc., 77, 4111 (1955), refers to the synthesis of the 6-cis-vitamin A acid through the Knoevenagel condensation reaction of β-ionylideneacetaldehyde with an ester of β-methylglutaconic acid catalyzed by a weak base. German Patent No. 1,050,763 and R . Trav. Chim., 68, 609 (1949) refer to the synthesis of the 9-cis form of vitamin A, as the minor isomer, utilizing the Reformatsky and Wittig condensation reactions, respectively.

The present method exploits the highly crystalline nature of 9-cis retinoic acid to enrich it from a mixture of isomers produced by the photolysis of any isomer of retinoic acid.

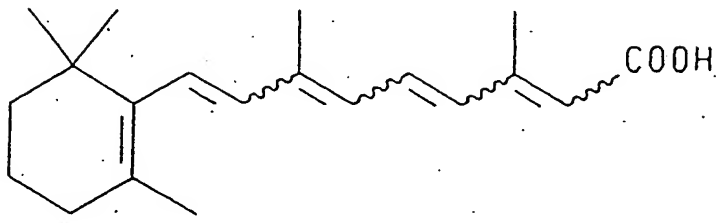
Summary of the Invention

The present invention relates to a method for the preparation of a compound of the formula



II

comprising photolyzing a compound of the formula

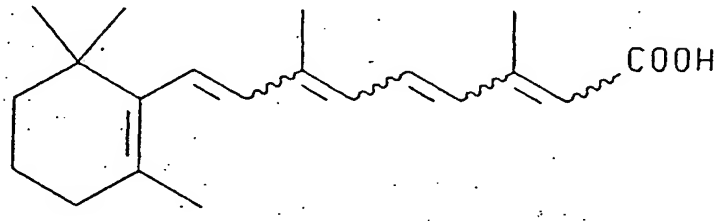


I

The present invention also relates to a method of crystallizing 9-cis retinoic acid directly from the reaction solution.

Detailed Description of the Invention

The following reaction scheme illustrates the preparation of the compound of the present invention.



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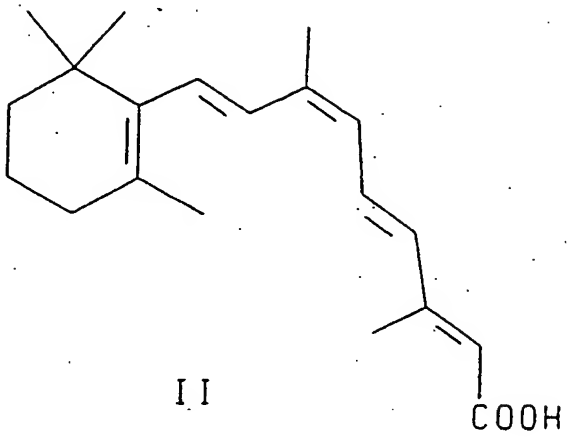


II

The retinoic acid compound of formula I is converted to the corresponding 9-cis retinoic acid of formula II by refluxing and photolyzing I in solvent, preferably for a time period between about 19 hours to about 29 hours, more preferably about 24 hours, under inert reaction conditions. Photolysis of the trans retinoic acid compound of formula I occurs at wavelengths between about 250 nanometers to about 380 nanometers, preferably about 345 nanometers, through the use of a 150 watt to 300 watt tungsten filament lamp. Acetonitrile is the preferred solvent, however, other suitable solvents include C_1-C_5alkanol, ethyl acetate, tetrahydrofuran, dioxane, carbon tetrachloride, ethylene glycol dimethyl ether and dimethylacetamide. Upon completion of this reaction step, the reaction mixture is allowed to cool to room temperature and the desired 9-cis retinoic acid compound of formula II is recovered from solution in the form of a crystalline precipitate.

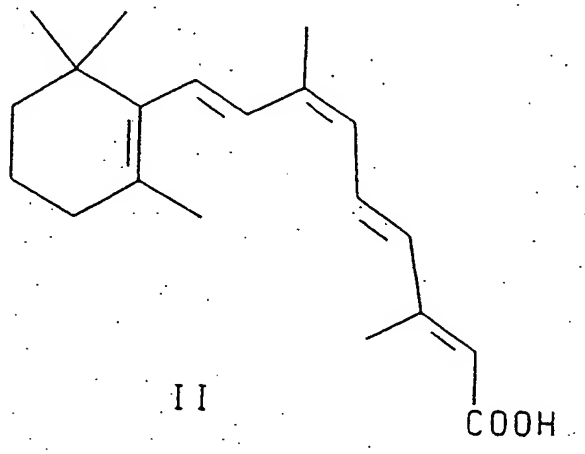
The 9-cis retinoic acid compound is useful in the treatment of dermal, neoplastic and immunological disorders.

EXAMPLE 1

Trans-retinoic acid (4.0 grams, 13.3 mmol) was dissolved in high pressure liquid chromatography grade acetonitrile (1.5 liters) in a 3-liter single neck flask equipped with a condenser, a nitrogen inlet tube and a magnetic stirrer. The stirred dispersion dissolved at reflux under exposure to a 300 Watt tungsten filament lamp for 24 hours. After cooling, the solvent was removed on a rotary evaporator (bath temperature 35-40°C, aspirator vacuum) until 800 mL of solvent has been collected. The reaction mixture was allowed to stand at ambient temperature for 30 minutes. Crystallization then began and was allowed to proceed for 10 minutes. Filtration provided 564 mg of a yellow solid. Recrystallization from ethanol provided 197 mg of 9-cis retinoic acid (m.p. 187-189°C, ethanol), 5% yield. Reequilibration of the mother liquors under the above conditions provided 177 mg of additional material.

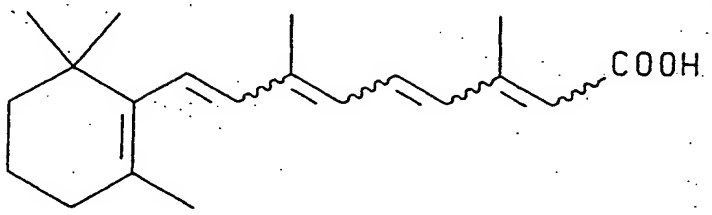
CLAIMS

1. A method of preparing a compound of the formula



II

comprising photolyzing a compound of the formula



I

2. A method according to claim 1, wherein the 9-cis retinoic acid of formula II is crystallized directly from the reaction solution.

3. A method according to claim 1, wherein the retinoic acid of formula I is trans retinoic acid.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 94/00595

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C403/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 026 778 (M. LALONDE ET AL.) 31 May 1977 see the whole document	1-3
X	CHEMICAL ABSTRACTS, vol. 119, no. 5, 2 August 1993, Columbus, Ohio, US; abstract no. 049677, DAWSON M I ET AL 'Preparation of 9-cis-retinoic acid [11,12-3H(N)] by photochemical isomerization' see abstract & J. LABELLED COMPD. RADIOPHARM. (JLCRD4,03624803);93; VOL.33 (3); PP.245-7 SRI INT.;MENLO PARK; 94025; CA; USA (US)	1,3

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1

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 1994	28.04.94

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

[redacted]rmation on patent family members

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		AT-B- 350743	11-06-79
		BE-A- 835334	07-05-76
		DE-A,B,C 2548883	13-05-76
		FR-A,B 2291191	11-06-76
		GB-A- 1527909	11-10-78
		JP-C- 1240842	26-11-84
		JP-A- 51070749	18-06-76
		JP-B- 59015907	12-04-84
		NL-A- 7512152	14-05-76